What is claimed is:

1. A method for the preparation of macrocyclic molecules comprising:

contacting purified excised TE domain protein with a substrate that comprises an activated acyl residue and a pendant nucleophile separated by a linear backbone under conditions conducive to formation of a TE-O-acyl bond such that subsequently the pendant intramolecular nucleophile can displace the TE domain to form the macrocyclic product.

2. A macrocyclization method as in claim 1 wherein the contacting of the excised TE domain protein with a substrate occurs in a medium that comprises at least 90 % water.

3. A macrocyclization method as in claim 2, wherein the contacting of the excised TE domain protein with a substrate occurs in a medium that comprises at least 95 % water.

4. A macrocyclization method as in claim 2, wherein the non-water component(s) is a polar, weakly-nucleophilic organic solvent.

5. A macrocyclization method as in claim 1, wherein the contacting of the excised TE domain protein with a substrate occurs in an aqueous solution comprising one or more buffers or other organic or inorganic salts.

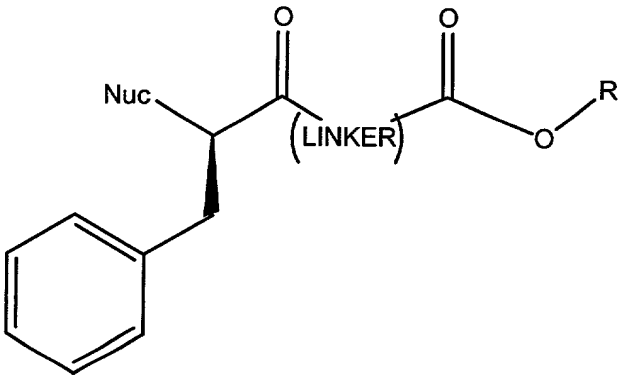
6. A macrocyclization method as in claim 1, wherein the pH of the reaction solution is in the range of about 5 to about 9.

7. A macrocyclization method as in claim 6, wherein the pH of the reaction solution is in the range of about 6 to about 8.

8. A macrocyclization method as in claim 6, wherein the pH of the reaction solution is about 7.

9. A macrocyclization method as in claim 1, wherein the activated acyl residue is an activated ester functional group.

10. A macrocyclization method as in claim 9, wherein the substrate can be represented by the formula:

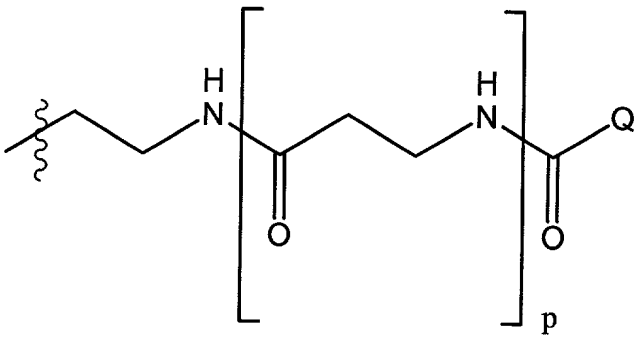


wherein

Nuc is chosen from NH_2, OH or SH;

LINKER is a peptidic sequence, synthetic hydrocarbon group or a combination thereof connecting the thioester and the 2-(Nuc)-3-phenyl-propionyl residue, the LINKER comprises a linear backbone of at least 14 atoms; and

R is a group that can be represented by the formula:



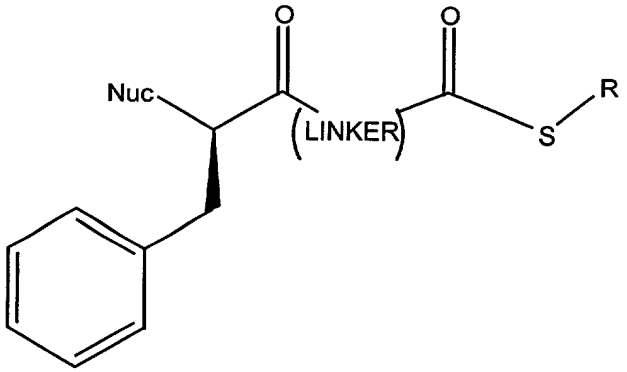
wherein Q is a group having between about 4 carbon atoms and about 20 carbon atoms and between about 0 and 10 hetero atoms selected from N, O or S, which can optionally be

tethered to a solid support, where each carbon of the linear backbone may be optionally substituted with 0, 1, or 2 groups selected from C_{1-6}alkyl, hydroxy, amino, halogen, C_{1-6}alkoxy, or oxo; and

p is an integer from 0 to about 2.

11. A macrocyclization method as in claim 1, wherein the activated acyl residue is an activated thioester functional group.

12. A macrocyclization method as in claim 11, wherein the substrate can be represented by the formula:



wherein:

Nuc is chosen from NH_2, OH or SH;

LINKER is a peptidic sequence, synthetic hydrocarbon group or a combination thereof connecting the thioester and the 2-(Nuc)-3-phenyl-propionyl residue, the LINKER comprises a linear backbone of at least 14 atoms; and

R is an optionally substituted C_{1-12} alkyl group.

13. A macrocyclization method as in claim 12, wherein the substrate is sufficiently polar such that its solubility and that of the resulting macrocycle molecule in the aqueous reaction medium is at least 0.1 g/L.

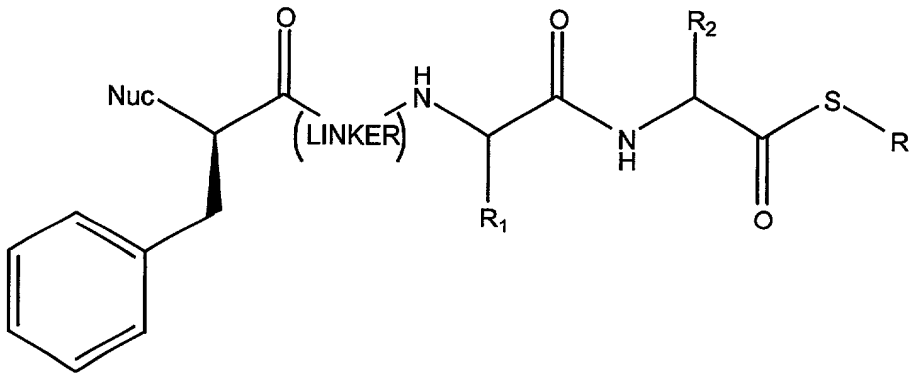
14. A macrocyclization method as in claim 12, wherein R is a N-C_2-C_6alkanoylC_2-C_6aminoalkyl.

15. A macrocyclization method as in claim 14, wherein the substrate leaving group, SR, is N-acetylcysteamine (SNAC).

16. A macrocyclization method as in claim 12, wherein Nuc is NH_2.

17. A macrocyclization method as in claim 12, wherein Nuc is OH.

18. A macrocyclization method as in claim 12, wherein the substrate can be represented by the formula:



wherein

Nuc is chosen from NH_2, OH or SH; .

LINKER is a peptidic sequence, synthetic hydrocarbon group or a combination thereof connecting the thioester and the 2-(Nuc)-3-phenyl-propionyl residue, the LINKER comprises a linear backbone of at least 6 atoms;

R is as defined for Claim 12; and

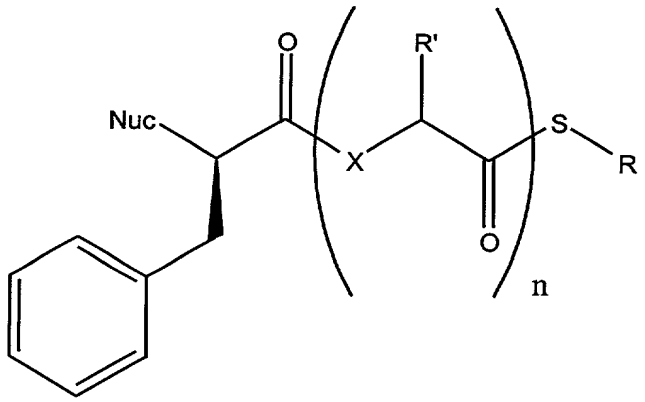
R_1 and R_2 are chosen from the side chain substituents of the synthetic and biosynthetic amino acid residue side chains and each residue can have either D or L stereoconfiguration. R_1 and R_2 are chosen independently and can be the same or different.

19. A macrocyclization method as in claim 18, wherein the substrate is sufficiently polar such that its solubility and that of the resulting macrocyclic molecule in the aqueous reaction medium is at least 0.1 g/L.

20. A macrocyclization method as in claim 18, wherein R_1 is a synthetic or biosynthetic amino acid residue side chain substituent that is charged at about pH 7 including a substituted C_1-C_6aminoalkyl group.

21. A macrocyclization method as in claim 20, wherein R_1 is L-3-aminopropyl.

22. A macrocyclization method as in claim 12, wherein the substrate can be represented by the formula:



wherein:

Nuc is chosen from NH_2 or OH;

n is an integral number greater than or equal to 5;

X is independently chosen from O and NH for each occurrence of X;

R is an optionally substituted N- C_2-C_6alkanoylC_2-C_6aminoalkyl;

R' is independently chosen for each occurrence for R' from the side chain substituents of the synthetic and biosynthetic amino acid residue side chains and each amino acid residue can have either D or L stereoconfiguration.

23. A macrocyclization method as in claim 22, wherein:

Nuc is NH_2; and

X is NH for each occurrence of X in the substrate.

24. A macrocyclization method as in claim 22, wherein:

Nuc is NH_2; and

X is chosen from O and NH for each occurrence of X in the substrate such that at least one occurrence of X in the substrate is O.

25. A macrocyclization method as in claim 22, wherein:

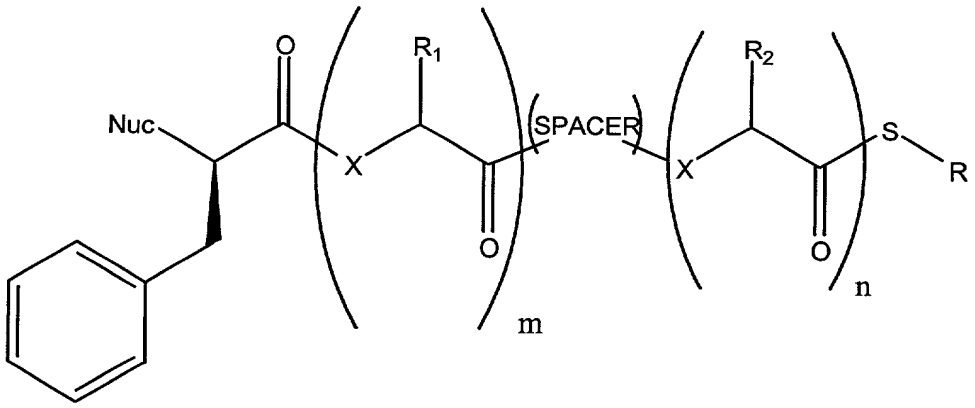
Nuc is OH; and

X is NH for each occurrence of X in the substrate.

26. A method as in claim 22, wherein n is between 5 and about 15 inclusive.

27. A method as in claim 22, wherein at least one occurrence of R' is 3-aminopropyl.

28. A macrocyclization method according to claim 12, wherein the substrate that comprises at least one non-peptidic spacer can be represented by the formula:



wherein:

Nuc is chosen from NH_2 or OH;

m and n are non-negative integers;

X is independently chosen for each occurrence of X in the formula to be either O or NH;

SPACER is a group of atoms or functional group residues that are not amino acid residues or depsi residues that comprise z atoms in the linear backbone of the substrate;

z is an integral number greater than or equal to about 4; and

the sum of z + 3m + 3n is between about 12 and 36.

29. A macrocyclization method as in claim 28, wherein the substrate is sufficiently polar such that its solubility and that of the resulting macrocyclic molecule in the aqueous reaction medium is at least 0.1 g/L.

30. A macrocyclization method as in claim 28, wherein z is about 6 to about 24.

31. A macrocyclization method as in claim 28, wherein the non-peptidic SPACER(s) comprises one or more of the following substituted groups such that the total number of atoms, z, in the linear backbone of the SPACER is greater than about 6: C_3-C_{12}-alkyl, C_3-C_{12}-alkenyl, C_3-C_{12}-alkynyl, C_3-C_7-cycloalkyl, C_3-C_7-heteroalicyclic, aryl, heteroaryl, amine, C_1-C_{12}-alkylamino, amide, ester, ketone, sulfoxide, ether, thioether, imine, sulfone, and the like.

32. A macrocyclization method as in claim 28, wherein the non-peptidic SPACER(s) comprises one or more of the following functional groups such that the total number of atoms, z, in the linear backbone of the SPACER is greater than about 6: α,ω-alkandiyl, α,ω-alkane diol, α,ω-alkane diamine, ω-(1-alkanol)amine, ω-hydroxyalkanoate or ω-aminoalkanoate such that two or more functional groups are linked by bonds chosen from the group of ether, amine, amide or ester bonds where each bond is independently chosen for each linkage.

33. A macrocyclization method as in claim 32, wherein the non-peptidic SPACER comprises one or more of the following functional groups linked together by either an amide or ester bond each bond being independently chosen at each occurrence: glycine, glycolate, O-(2-aminoethyl)glycolate, O-(2-ethanol)glycolate, O-(2-(2-aminoethoxy)ethyl)glycolate, O-(diethylene glycol)glycolate, and the like.

34. A macrocyclization method comprising the steps of:

elongating a substrate, which essentially can not be cyclized by an excised TE domain protein, by contacting excised TE domain protein with a first substrate under conditions conductive to formation of a TE-O-acyl substrate intermediate such that subsequently an intermolecular recognition element nucleophile from a second, identical or different, substrate can displace the TE domain to form an elongated substrate homodimer or an elongated substrate heterodimer;

repeating the elongating step until the intermediate substrate oligomer is of sufficient length to undergo macrocyclization catalyzed by excised TE domain protein; and

contacting the elongated substrate dimer with excised TE under conditions conductive to formation of a TE-O-acyl substrate dimer intermediate such that subsequently an intramolecular recognition element nucleophile can displace the TE domain to form the macrocyclic product.

35. A macrocyclization method as in claim 34, wherein the contacting of the excised TE domain protein with a substrate occurs in a medium that comprises at least 90 % water.

36. A macrocyclization method as in claim 34, wherein the contacting of the excised TE domain protein with a substrate occurs in a medium that comprises at least 95 % water.

37. A macrocyclization method as in claim 34, wherein the non-water component(s) is a polar, weakly-nucleophilic organic solvent.

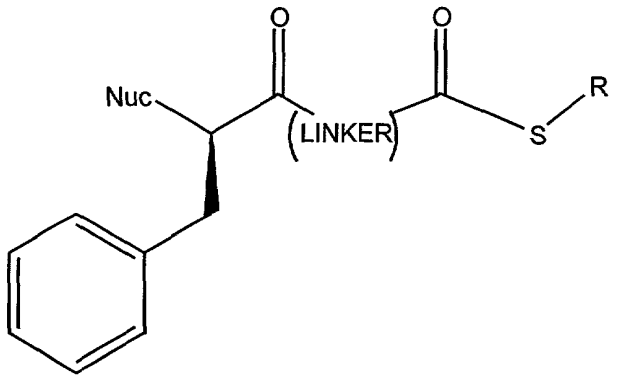
38. A macrocyclization method as in claim 34, wherein the contacting of the excised TE domain protein with a substrate occurs in an aqueous solution comprising one or more buffers or other organic or inorganic salts.

39. A macrocyclization method as in claim 34, wherein the pH of the reaction solution is in the range of about 5 to about 9.

40. A macrocyclization method as in claim 39, wherein the pH of the reaction solution is in the range of about 6 to about 8.

41. A macrocyclization method as in claim 39, wherein the pH of the reaction solution is about 7.

42. A macrocyclization method as in claim 34, with a substrate according to the formula:



wherein:

Nuc is chosen from NH_2 or OH;

LINKER is a group of atoms or functional group residues connecting the thioester and the 2-(Nuc)-3-phenyl-propionyl residue and LINKER comprises a linear not more than 14 atoms; and

R is N-C_{2-6}alkanoylC_{2-6}aminoalkyl group.

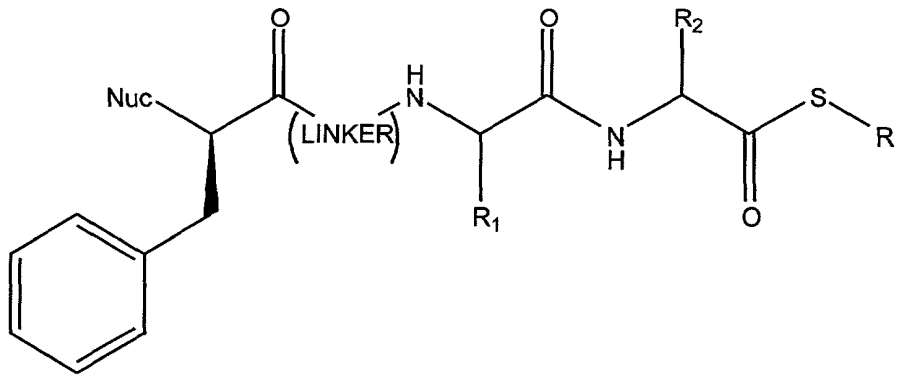
43. A macrocyclization method as in claim 42, wherein the substrate is sufficiently polar such that its solubility and that of the resulting macrocyclic molecule in the aqueous reaction medium is at least 0.1 g/L.

44. A macrocyclization method as in claim 42, wherein the substrate leaving group, SR, is N-acetylcysteamine (SNAC).

45. A macrocyclization method as in claim 42, wherein the substrate Nuc is NH_2.

46. A macrocyclization method as in claim 42, wherein the substrate Nuc is OH.

47. A macrocyclization method as in claim 42, wherein the substrate can be represented by the formula:



wherein

Nuc is chosen from NH_2 or OH;

LINKER is a group of atoms or functional group residues connecting the thioester and the 2-(Nuc)-3-phenyl-propionyl residue, the LINKER comprises a linear backbone of not more that 9 atoms;

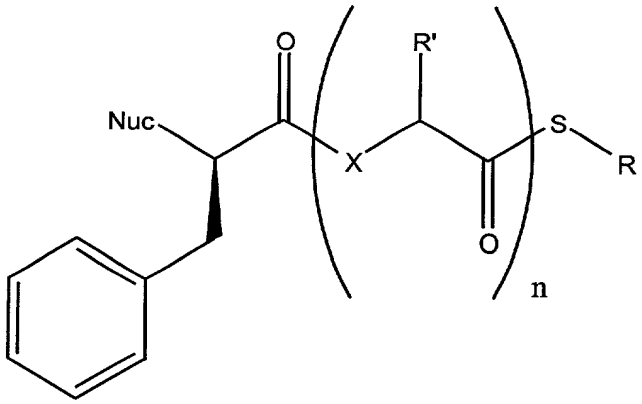
R is as defined for Claim 42; and

R_1 and R_2 are chosen from the side chain substituents of the synthetic and biosynthetic amino acid residue side chains and each residue can have either D or L stereoconfiguration. R_1 and R_2 are chosen independently and can be the same or different.

48. A macrocyclization method as in claim 46, wherein R_1 is a synthetic or biosynthetic amino acid residue side chain substituent that is charged at about pH 7 including a substituted C_1-C_6aminoalkyl group.

49. A macrocyclization method as in claim 48, wherein R_1 is L-3-aminopropyl.

50. A macrocyclization method as in claim 42, wherein the substrate can be represented by the formula:



wherein:

R is as defined in Claim 42;

Nuc is chosen from NH_2 or OH;

n is an integral number greater than or equal to 5;

X is independently chosen for each occurrence of X from O and NH; and

R' is independently chosen for each occurrence for R' from the side chain substituents of the synthetic and biosynthetic amino acid residue side chains and each amino acid residue can have either D or L stereoconfiguration.

51. A macrocyclization method as in claim 50, wherein:

Nuc is NH_2; and

X is NH for each occurrence of X in the substrate.

52. A macrocyclization method as in claim 50, wherein:

Nuc is NH_2; and

X is chosen from O and NH for each occurrence of X in the substrate such that at least one occurrence of X in the substrate is O.

53. A macrocyclization method as in claim 50, wherein:

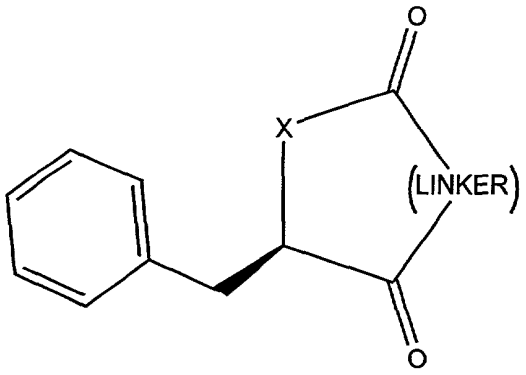
Nuc is OH; and

X is NH for each occurrence of X in the substrate.

54. A method as in claim 50, wherein n is between 1 and about 5.

55. A method as in claim 50, wherein at least one occurrence of R' is 3-aminopropyl.

56. A macrocylic compound that can be represented by the formula:

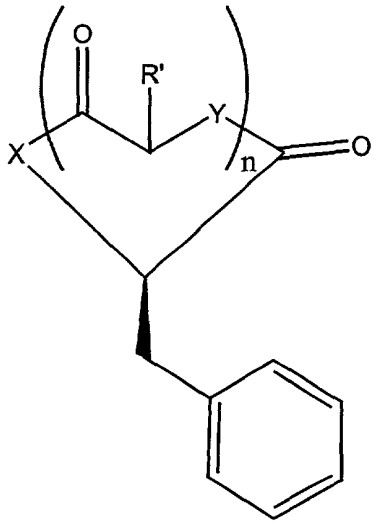


wherein:

LINKER is a peptidic sequence, synthetic hydrocarbon group or a combination thereof connecting the thioester and the 2-(Nuc)-3-phenyl-propionyl residue, the LINKER comprises a linear backbone of at least 14 atoms; and

X is chosen from S, O, or NH.

57. A macrocyclic molecule according to claim 56, wherein the macrocyclic molecule can be represented by the formula:



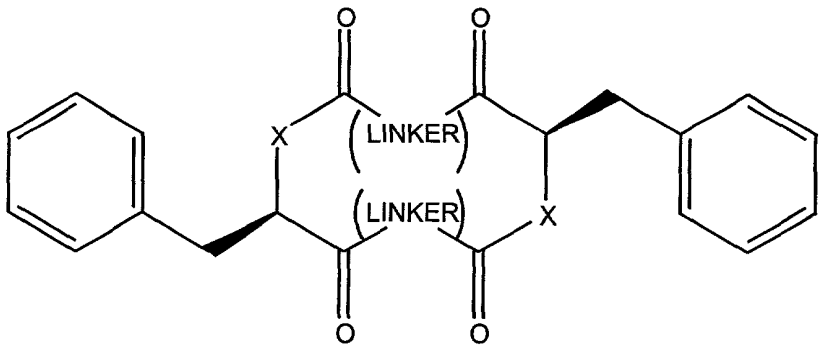
wherein:

n is an integral number greater than or equal to 5;

Y is independently chosen from NH or O for each occurrence of Y; and

R' is independently chosen for each occurrence for R' from the side chain substituents of the synthetic and biosynthetic amino acid residue side chains and each amino acid residue can have either D or L stereoconfiguration.

58. A macrocylic compound that can be represented by the formula:

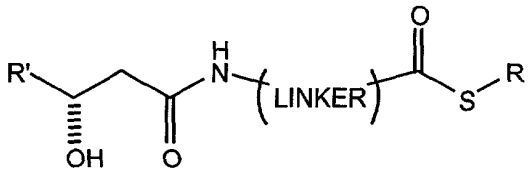


wherein:

LINKER is a group of atoms or functional group residues, connecting the thioester and the 2-(Nuc)-3-phenyl-propionyl residue, and LINKER has a linear backbone that comprises not more than 14 atoms; and

X is chosen from O, S and NH.

59. A macrocyclization method according to claim 1, wherein the substrate can be represented by the formula:



wherein:

LINKER is a peptidic sequence, synthetic hydrocarbon group or a combination thereof connecting the thioester and the 2-(Nuc)-3-phenyl-propionyl residue, the LINKER comprises a linear backbone of at least 14 atoms;

R is an optionally substituted C_{1-12} alkyl group; and

R' is a C_1-C_{18} alkyl group or a lipophilic group.